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Alterations in Systemic Vascular Volume of the Dog in Response to Hexamethonium and Norepinephrine[1]

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ABSTRACT

ROSE, JOHN C. AND EDWARD D. FREIS. *Alterations in systemic vascular volume of the dog in response to hexamethonium and norepinephrine.* Am. J. Physiol. 191(2): 283–286. 1957.—A diaphragm pump of controlled constant output was substituted for the left ventricle in dogs. Left auricular blood was conducted to a reservoir, from which it was pumped into the thoracic aorta. Left ventricular by-pass was complete. Alterations in total vascular volume were continually monitored by observation of the pump reservoir level. Sympathetic blockade (hexamethonium) increased total vascular volume (mean 15%). This resulted in decreased venous return and decreased right ventricular output. Norepinephrine constricted the total vasculature and decreased vascular volume (mean 12%). This resulted in increased venous return and cardiac output. These experiments demonstrated the complex integrated responses of the total circulation to sympathetic vasomotor activity. The role of the sympathetic nervous system not only in the regulation of arteriolar tone and cardiac activity but also in adjusting total vascular volume and venous return was emphasized. Venous return, and hence cardiac output alterations accompanying systemic vasomotor activity can only be detected by continuous methods of flow measurement.

RECENT studies suggest that systemic vasomotor activity alters the distribution of blood between the systemic and pulmonary circulations. Calculations of the Hamilton 'central blood volume' and the Newman 'lung blood volume' have revealed a decrease with systemic vasodilatation due to spinal anesthesia (1) and an increase with norepinephrine infusion (2). Using a continuous gravimetric technique in dogs, Sarnoff and his colleagues demonstrated increased lung weight following the systemic hypertension occurring with intracisternal injection of fibrinogen and thrombin (3); the increase was abolished by ganglionic 'blockade.' Rashkind and his coworkers noted an increase in directly measured venous return, and a decrease in systemic vascular volume following injection of pressor amines (4).

These observations are of fundamental importance in clarifying the integrated responses of the circulation to sympathetic stimulation and inhibition. The role of the sympathetic nervous system in the regulation of arteriolar tone is well known. The investigations cited emphasize the importance of these nerves in the adjustment of intravascular volume. This function of the sympathetic nervous system is less well appreciated.

The present report is concerned with the direct measurement of alterations in intravascular volume using an extracorporeal left ventricular pump of constant controlled output in dogs (5). Continuous monitoring of the pump reservoir in this experimental system permitted accurate sequential measurements of systemic vascular volume following vasoconstriction and vasodilatation. These observations have led to a fuller appreciation of the total hemodynamic effects of systemic vasomotor activity (6).

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MATERIALS AND METHODS

Dogs weighing between 13 and 19 kg were anesthetized with sodium pentobarbital, 25 mg/kg. Respirations were maintained with 100% oxygen administered by a variable-phase pulmotor valve to an endotracheal cannula. The surgical procedure used to by-pass the left ventricle with the extracorporeal pump has been described in detail (5).

The pump contains a 12-inch plastic diaphragm which serves as a partition between the blood and the heavy oil hydraulic medium. The pump rate can be varied from 35 to 280 strokes/min. and the stroke volume from 0 to 160 ml/stroke, independently of the rate. The output remains constant despite large changes in resistance to outflow. In these experiments, the operating output range was 1.6–2.6 l/min.

Blood was drained from the left auricle through a ⅜″ I.D. plastic (Tygon) tube to a plastic reservoir of 1.5 liters capacity. From the reservoir it was pumped to a T-tube in the descending thoracic aorta. Left ventricular by-pass was complete in all experiments. The right ventricle was not by-passed and continued to function normally. No studies are reported in dogs with failing right ventricles, evidenced in this preparation by venous hypertension, dilated heart and increased intravascular volume (7).

Aortic pressure and pulmonary arterial pressure were measured continuously using strain-gage transducers, carrier wave amplifiers and a four-channel direct-writing oscillograph. Right ventricular output was monitored in the left auricular drainage tube using a Shipley-Wilson rotameter. However, flow was determined with greater precision using timed visual recordings of reservoir level. Reservoir level alterations per unit time were compared with the known pump output. Shifts of blood between the reservoir and the intravascular space were determined by recording reservoir level every 5 seconds during the experimental period.

Hexamethonium (1.3–3.9 mg/kg) was injected intravenously as a single dose to inhibit sympathetic transmission at the ganglia. Norepinephrine (1.6–7.7 μg/kg) was injected intravenously in a single dose to mimic sympathetic stimulation. Drugs were injected only when the reservoir level was unchanging; i.e., right ventricular output equalled 'left ventricular' pump output.

TABLE 1. DATA FROM 9 EXPERIMENTS IN WHICH HEXAMETHONIUM (C6) AND NOREPINEPHRINE WERE ADMINISTERED IN SEQUENCE TO DOGS MAINTAINED WITH THE MECHANICAL LEFT VENTRICLE

Pump Output	Dose C6	Max. ΔV*	Max. ΔP†	Dose Nor.	Max ΔV*	Max ΔP†
l/min.	*mg/kg*	*ml*	*mm Hg*	*μg/kg*	*ml*	*mm Hg*
Dog, 1, 12.0 kg						
1.6	2.0	+150	−28	1.7	−150	+60
Dog 2, 13.3 kg						
1.9	1.8	+250	−12	1.6	−150	+70
Dog 3, 13.5 kg						
1.9	2.0	+125	−12	3.7	−75	+40
Dog 4, 19.0 kg						
2.1	1.3	+225	−30	1.5	−75	+42
Dog 5, 13.0 kg						
2.2	3.9	+115	−30	7.0	−105	+70
Dog 6, 14.5 kg						
2.6	1.7	+200	−24	3.5	−100	+25
Dog 7, 18.5 kg						
2.2	1.3	+125	−25	5.2	−60	+45
Dog 8, 13.0 kg						
2.2	1.9	+275	−8	7.7	−325	+32
Dog 9, 13.0 kg						
2.2	1.9	+150	−16	2.5	−150	+50

* Max. ΔV = Maximum alteration in intravascular volume following drug injection.

† Max. ΔP = Maximum systemic arterial pressure change following drug injection.

RESULTS

Data from nine experiments in which hexamethonium (C6) and norepinephrine were administered in sequence are given in table 1. Figure 1 shows a typical experiment.

Following administration of C6, the systemic arterial pressure fell. This was followed by a more gradual reduction in pulmonary arterial pressure and a fall in the reservoir blood level. The reservoir level alteration was usually complete within 5 minutes or less, at which time the intravascular volume of the dog was increased by 7–21 ml/kg body weight. Assuming an average blood volume of 85 ml/kg body weight (9), this gain in intravascular volume represents a mean of 15 per cent of total blood volume (range 8–25). Pressure in the inferior vena cava did not change significantly.

Systemic hypotension due to hexamethonium always preceded the reduction in pulmonary arterial pressure and right ventricular output by 10–30 seconds. Occasionally, as

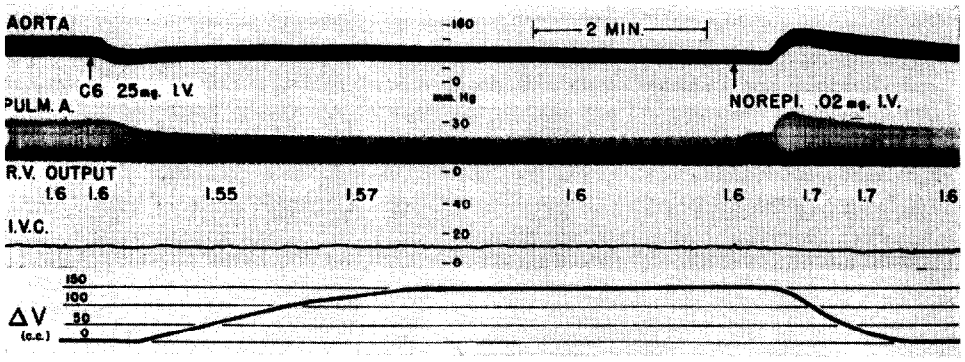

FIG. 1. Actual record of experiment in *dog 1*, in which hexamethonium (2 mg/kg) intravenously was followed in 7½ min. by norepinephrine (1.7 μg/kg) intravenously. (Right ventricular output is given in l/min.) Following hexamethonium, aortic pressure decreased, followed in 15 sec. by the fall in pulmonary arterial pressure. ΔV indicates blood transfer from pump reservoir to vascular system, and back again. The initial small rise in pulmonary arterial pressure following norepinephrine was due to direct pulmonary vasoconstriction (8).

shown in figure 1, some recovery of systemic arterial pressure from the initial fall was noted during the period of declining pulmonary arterial pressure and right ventricular output.

Following norepinephrine injection, systemic and pulmonary arterial pressures rose, and the reservoir volume increased. The reservoir level rise was transient and of shorter duration than the change produced by hexamethonium. It reached its maximum within 2 minutes and thereafter declined gradually. The range of decreases in intravascular volume produced by norepinephrine was wide, 3–25 ml/kg body weight. This represented a mean of 12% (range 4–29) of the assumed total blood volume (85 ml/kg). Inferior vena caval pressure alterations were variable, sometimes falling significantly at the height of response.

Norepinephrine injections not preceded by hexamethonium produced responses that were no different qualitatively from those that were given after hexamethonium.

DISCUSSION

It is evident that reservoir volume alterations in this experiment were mediated through changes in right ventricular output, since left ventricular (pump) output remained constant. Right ventricular output was dependent on venous return, and alterations in venous return were due to changing peripheral vascular volume. The preparation of Rashkind and his co-workers (4) permitted similar conclusions, although right ventricular output was maintained at a constant level with a pump drawing from a venous reservoir.

Following the ganglionic blocking agent, an increased size of the systemic vascular tree resulted in decreased venous return, decreased right ventricular output and lowered reservoir level. The retention of blood could not have been due to cardiac failure since the central venous pressure did not rise.

Norepinephrine constricted the systemic circulation, 'squeezed' excess blood into the right heart, increased right ventricular output and raised the reservoir level. In contrast to hexamethonium, part of this effect was cardiac in origin since the central venous pressure frequently decreased. As previous studies (1–4) indicate, in the intact animal, blood shifts of this degree most likely are into and out of the pulmonary vascular bed.

The observed changes in vascular capacity seem too large to explain on the basis of altered arteriolar tone alone. Several recent investigations attest to the autonomic control of venomotor tone as well (10–12).

These experiments explain the hemodynamic responses of man to ganglionic blockade (13). In the absence of heart failure, arterial pressure reduction was accompanied by decreased cardiac output and decreased right heart pressures. It is reasonable to conclude that increased systemic vascular volume accounted for the reduction of venous return. However, it seems incorrect to conclude that the action of hexamethonium is solely on the 'venous side' of the circulation (14).

The fact that the systemic arterial pressure fell before the major reduction in pulmonary arterial pressure and right ventricular output indicates that the initial response to hexamethonium was a decrease in total peripheral resistance. This was followed, within 1 minute, by reduction of cardiac output due to diminished venous return. Relaxation of arterioles and then postarteriolar vessels (active or passive), followed by failure of venous return are rapid adjustments that probably cannot be detected except with the use of continuous methods of measurement. Trapold observed the effects of ganglionic blocking agents on pressure and flow in the mesenteric vascular bed of dogs (15). He concluded similarly that both arteriolar and venous tone are reduced. He suggested that when reduction in arteriolar tone predominates, total peripheral resistance will decrease; when reduction in venous tone predominates total peripheral resistance either remains unchanged or increases.

Using the pulse contour method for determining cardiac output in dogs, Moyer, Huggins, Handley and Mills (16) observed a transient rise in cardiac output at the onset of the hypotensive effect of hexamethonium. This was followed by a gradual decline to levels below the control valves. Using the Fick principle for determination of cardiac output in man (13) (which cannot follow rapid sequential changes), we were led to conclude that the reduction of arterial pressure following hexamethonium was accomplished solely by failure of venous return and diminished cardiac output. These conclusions should be modified to include an initial decrease of total peripheral resistance.

Fowler and his colleagues (17) noted increased pressures in the lesser circulation during norepinephrine infusions in human subjects. Goldenberg (18) and others (2) have noted no increase in cardiac output in man and animals during norepinephrine infusion. Since systemic vasoconstriction and vasodilation alter the capacity of the systemic vasculature, there must be a transient alteration in right ventricular output (i.e., increase with constriction, decrease with dilatation) during the period of blood redistribution. These measurements also can be made best by using continuous recording techniques. In addition, the magnitude of flow change necessary to produce large blood shifts may be within the limits of error of the Fick and indicator-dilution methods (fig. 1).

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